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EXAMINER
GUEST, S

ART UNIT	PAPER NUMBER
1812	8

DATE MAILED: 03/09/92

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 12/16/91 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 25-27, 30-41 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 1-24, 28-29 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 25-27, 30-41 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

The following rejections are withdrawn in light of applicant's amendment and arguments filed in paper number 7: 1) the rejection made under 35 USC 101 for non-statutory subject matter, 2) the rejection made under 35 USC 112, 1st paragraph and 35 USC 101 for lack of in vivo data, 3) the rejection of claims 30-41 made under 35 USC 112, 2nd paragraph in regards to the term "substantially", 4) the rejection made under 35 USC 102b/103 over Heldin et al., Johnsson et al., Antoniades et al., and 5) the rejection made under 35 USC 103.

The following rejections are maintained for the reasons stated below and in the previous office: 1) the rejections made under 35 USC 112, 1st paragraph for lack of enablement, 2) the rejection made under 35 USC 112, 2nd paragraph in regards to the term "recombinant", and 3) the rejection made under 35 USC 102e over Murray, and 4) the rejection made under 35 USC 102(a) over Betsholtz.

Claims 25-27 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to the A-chain of PDGF depicted in the figure 1 or 2. Claims 25-27 recite "..or analog of said sequence that is substantially homologous and functionally equivalent thereto" which is overly broad since many proteins could have meet this definition, and be entirely different proteins in structure but are not disclosed. The

specification defines "substantially homologous" as less than 10 amino acid substitutions or deletions, however no guidance is provided as to where within the protein these substitutions and deletions can be made. Therefore, the scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species.

Applicants' have argued that the functional limitation, i.e. that the protein must be "functionally equivalent" to PDGF, effectively excludes inoperative embodiments. However, applicants have provided no guidance of which of the numerous claimed proteins might possess PDGF activity. Predictability of which changes can be tolerated in a protein's amino acid sequence <u>while retaining similar activity/utility</u> (as required by the functional limitation in the claim) requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex.

While recombinant and mutagenesis techniques are known and it is known that some proteins can tolerate a number of amino acid substitutions (i.e. predominantly in non-conserved amino acids), the positions within the

protein's sequence where such amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity/utility are limited and such modifications are unpredictable in the absence of further guidance. Other positions in the sequence of such proteins are critical to the protein's structure/function relationship, e.g. such as various positions or regions directly involved in binding, catalysis or other activity and in providing the correct three-dimensional spacial orientation of binding and/or catalytic sites. It is well known that such critical positions can tolerate only conservative substitutions or no substitutions and one skilled in the art would expect any tolerance of a given protein to modification to decrees with each further and additional modification, e.g. multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acids modification in such proteins. However, even if it were shown that some modifications could be tolerated in the claimed proteins, for the reasons discussed the claims would still expectedly encompass a significant number of inoperative species which could not be distinguished without undue experimentation.

While enablement can be supported even if some experimentation is required, such experimentation must be merely routine and if the results to be obtained are unpredictable the experimentation is not routine, but rather undue. Applicants have not taught where the critical regions are in the instant proteins or related proteins having the same utility nor what amino acids are conserved in the particular claimed proteins nor the structural requirements for producing compounds of similar activity/utility. Thus, beyond the mere presentation of sequence data, applicants have provided little

or no guidance which would, without undue experimentation, enable one of ordinary skill in the art to determine what positions, if any, in the protein are tolerant to change (e.g. such as by amino acid substitutions), the nature and extent of changes that can be made and tolerated in the various positions and what utility will be possessed by the modified proteins, particularly in view of the virtually infinite number of compounds encompassed by these claims wherein the polypeptide can include any number of addition, deletions or substitutions. Without such guidance, the changes which can be made in the proteins structure and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986). For a more recent analysis of these principles, see Amgen v. Chugai, 18 USPQ 2d 1016 (Fed. Cir. 1991), In re Wands 8 USPQ 2d 1400 (Fed. Cir. 1988), and In re Vaeck 20 USPQ 1438 (Fed. Cir. 1991).

Claims 30-40 are rejected under 35 U.S.C. 112, first paragraph as failing to enable any person skilled in the art to which it pertains to make and use the claimed products. Applicant is claiming a series of fragments of the protein claimed in claim 25, with 6 unspecified substitutions at specified locations in the PDGF A chain. The claims are non-enabled for the basically the same reasons presented in the above rejection. There are an extreme large number of proteins broadly encompassed by the claims, and there are a significant number of inoperative species.

Claims 25-27, and 30-41 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and

distinctly claim the subject matter which applicant regards as the invention. Claims 25-27 are confusing in the recitation of "recombinant". Applicants state in their response that the term "recombinant" is certainly well known in the art. However, it is maintained that the term is a very general, somewhat nebulous term, which could have many different connotations. Furthermore, applicants have defined the term on page 4-5 as "intends DNA of genomic, cDNA, semisynthetic, or synthetic origin...". This is confusing since in the instant claims, "recombinant" is defining a protein, not DNA.

Claims 25-27, and 30-41 are rejected under 35 U.S.C. § 102(a) as being clearly anticipated by Betsholtz. The declaration filed in the parent application under 37 C.F.R. § 1.131 has been considered but is ineffective to overcome the Betsholtz reference. The evidence submitted is insufficient to establish a reduction to practice of the invention in this country prior to the effective date of the Betsholtz reference. First, all co-inventors must be co-declarants, or an explanation must be provided for why they could sign. Second, it is not clear who actually reduced to practice the claimed invention since the publication relied upon has more co-authors than the co-inventors. Therefore, there is no evidence that the inventors actually reduced to practice the claimed invention. Third, the notebook pages provided by N. Fong are not conclusive that the inventors reduced to practice the claimed invention since N. Fong is not one of the inventors. It is not clear what role N. Fong contributed to the invention.

Claims 25-27, and 30-41 are rejected under 35 U.S.C. § 102(e) as being clearly anticipated by Murray, pn 4889919. Murray claims the exact protein as applicants (see claims 1-12), and applicants state that this fact is not disputed, but provide a declaration under 37 CFR 131 to show relative dates of invention. The declaration filed in the parent application under 37 C.F.R. § 1.131 has been considered but is ineffective to overcome the Murray reference. The Murray reference is a U.S. patent that claims the rejected invention. An affidavit or declaration is inappropriate under 37 C.F.R. § 1.131(a) when the patent is claiming the same invention. The patent can only be overcome by establishing priority of invention through interference proceedings. See M.P.E.P. § 1101.02(g) for information on initiating interference proceedings.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon the filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shelly Guest whose telephone number is

(703) 308-3154. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

The location of the art unit in which this application is being handled has been changed. To aid in the correlation of papers, future papers should be marked "Art unit 1812".

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

DAVID L. LACEY
SUPERVISOR PRIMARY EXAMINER
ART UNIT 189A 180
3/6/92

sjg
March 6, 1992